REMARKS

Claims 28-34, and 49-91 constitute the pending claims in the present application. Applicants thank the Examiner and their supervisor for granting an interview on January 6, 2004. Applicants have amended claims 28, 49, 50, 51, 53, 65-68, 70, 71, 75-78, and 80-91. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 U.S.C. 103

Claims 28-34 and 49-91 are rejected under 35 U.S.C. 103(a) as being obvious over PCT/FR95/00520 (published on Nov. 16, 1995 as WO95/30759, or the '759 publication).

Specifically, the Office Action asserts that the '759 publication teaches nucleic acids encoding a chimeric serum albumin (SA) with a useful heterologous peptide inserted anywhere therein (emphasis added). The Office Action further contends that Carter and He teach the crystal structure of human SA, and therefore it would have been obvious to one skilled in the art to insert a biologically active peptide into one of the exposed loop regions.

Applicants respectfully traverse the Examiner's rejections. Applicants have amended independent claims 28, 49, 50 and 75 to clarify the subject matter. Support for the amendments may be found on page 2, first full paragraph, lines 1-3 and page 9, fourth full paragraph, of the specification.

Pursuant to MPEP 706.02(j), three basic criteria have to be met before a *prima facie* case of obviousness rejection can be made: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

First, Applicants contend that the prior art reference cited in the Office Action does not teach or suggest all the claim limitations of the pending claims. The pending claims recite two insertion sites for the biologically active peptide, from 360-369 and from 450-463. Neither one of these sites is specifically recited in the '759 publication. The '759 application teaches the following insertion sites on page 7 of the translation: 57-62, 103-120, 178-200 and 419-430.

Furthermore, the experimental section proposes specific insertions that are all contained within these regions that are distinct from the claimed regions, including at amino acid 58 (page 20, last paragraph), 187-190 (page 29, last paragraph), 186-191 (page 28, 1st full paragraph, and page 30 ,1st paragraph), 191-192 (page 27, last paragraph), 419-420 (page 26, last paragraph), and 420-429 (pages 20-21, bridging paragraph). Even though the crystal structure of human SA was known at the time of the '759 publication and was referenced in the '759 publication itself, the sites claimed in the present applications are distinct and non-overlapping with those in the publication. In fact, by suggesting insertion sites in spite of being aware of the crystal structure of human SA, the '759 publication teaches away from the recited insertion sites and thus away from the claimed invention, and in any event provides no motivation to choose any other insertion sites, such as those recited in the pending claims.

The Office Action also contends that "the specifically recited residues 360-369 in instant base claim 28 is loop connecting h9 and h10 of PCT/FR95/30759." Applicants contend that any conceivable insertion site, whether the 360-369 or any other, will be shown in Figure 1, as Figure 1 contains a diagram of the entire SA structure. The relevant point is that the '759 does not teach that residues 360-369 or the region between h9 and h10 provide an insertion site for a biologically active peptide, wherein the peptide retains the biological activity within the resulting chimera to interact with an organism and change a biological function of the organism.

Furthermore, Applicants point out that according to the structure of albumin described in Carter and He (Reference AE), on which the rejection arguments of the Office Action are based, insertion region 450-463 of the pending claims does not reside in a loop region of human SA. Instead, this insertion region resides exclusively within helix 4 of domain III, said helix extending from amino acids 445 to 463 of human SA. Accordingly, if anything, the teachings of the '759 publication, in light of the crystal structure of human SA described in Carter and He, would teach away from even attempting to insert a heterologous peptide within the claimed 450-463 region of human SA. Accordingly, Applicants contend that the choice of the claimed insertion sites, particularly the 450-463 site, would not have been obvious at the time of the invention.

Secondly, not only does the cited reference, alone or in combination with Carter and He, fail to teach or suggest all the limitations of the pending claims, it also fails to provide a

reasonable expectation of success. Applicants contend that a reasonable expectation of success with respect to the claimed invention refers to the expectation of success of being able to insert a biologically active peptide into regions 360-369 or 450-463 of SA with the resulting chimeric SA retaining the biological activity of the inserted peptide as presently claimed, and does not refer to the mere exercise of recombinantly inserting a peptide into SA.

Specifically, the '759 publication contains no working examples of a chimeric SA showing biological activity for the inserted peptide. The '759 provides two experimental examples of the purification from yeast of albumin proteins containing insertion of heterologous sequences. These chimeric proteins contain insertions of heterologous peptide at positions 186-191 and 187-190, respectively, which share no overlap with the claimed insertion sites. The purification yields are described on page 30, table 1 of the translation. No functional characterization is performed on the two proteins to test if the peptide retains biological activity *in vitro* or *in vivo*, no testing of the half-life of the proteins is disclosed, and no functional characterization of any kind is performed. Thus, these two examples amount to no more than a routine exercise in recombinant protein production, with no indication of a successful functional insertion of a biologically active peptide.

The last example of the '759 publication, on the last paragraph of page 30 of the translation, describes a hypothetical chimeric albumin protein containing a cleavage site for the factor Xa protease. In this hypothetical example, a protease cleavage site is inserted at amino acid 58, which is distinct from the insertion sited claimed in the present invention i.e. 360-369 and 450-463. This hypothetical example calls for the prophetic testing *in vitro*, under non-physiological salt and pH 8.0 conditions, for cleavage of the chimeric protein by a purified or recombinant factor Xa protease. No data or evidence is provided in this hypothetical example or anywhere else in the '759 reference that any insertions in albumin result in chimeric proteins that retain any biological activity, much less in the claimed regions. Accordingly, the '759 publication teaches no working examples of biologically active chimeric SA proteins. The '759 publication merely speculates on insertion sites that are distinct from those claimed in the present application, and never validates whether those sites allow an inserted polypeptide to retain biological activity. One skilled in the art would have had no reasonable expectation of success that a biologically active peptide inserted into SA, much less into regions 360-369 or

450-463 of SA, would result in a chimeric protein whose inserted peptide was biologically active under physiological conditions, such as those described in the present application where a chimeric protein is properly synthesized by a mammalian cell, secreted, and able to bind to the receptor on the surface of a cell and elicit a physiological response of modulating cell proliferation.

In light of the arguments presented, Applicants contend that a case of prima facie obviousness has not been presented by the Examiner, i.e., all the claim limitations are not taught or suggested by the cited reference, there is no motivation to select the particular features recited in the claims, and one skilled in the art would have had no reasonable expectation of success of arriving at the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Double Patenting

Claims 28-34 and 49-91 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33, and 54-104 of copending Application No. 09/768,183.

Applicants note that, pursuant to 37 CFR 1.130(b), a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome a provisional rejection based on a commonly owned co-pending application. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 212-497-3613. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully submitted,

By _____

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